Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-7, 9-10, 12-13, and 82-84 are pending in the application, with claims 1 and 12-13 being independent claims.

Claims 85-86 have been cancelled.

Claims 1, 12 and 13 have been amended without prejudice to or disclaimer of the subject matter therein.

It is believed that these changes introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and further request that they be withdrawn.

Rejections Under 35 U.S.C. § 112--Written Description

Claims 1-7, 9-10, 12 and 82-84 were rejected for allegedly failing to comply with the written description requirement. The Examiner based the rejection on two grounds: (1) the recitation of a mutation in one amino acid in SP1 or in the region of the CA-SP1 cleavage site that decreases inhibition of processing by DSB, and (2) the recitation of "a derivative." Applicants respectfully traverse the rejection.

Regarding the first ground for this rejection, Applicants have amended claims 1, 12 and 13 to recite that the mutation is A364V or A366V as compared to a reference sequence.

Regarding the second ground for this rejection, Applicants have amended the claims to omit the recitation of "derivative." Claim 1 now recites that the administered compound is a member of the betulin group or the betulinic acid group. Claim 12 now recites that the administered compound is a member of the dimethyl succinyl betulin group or the dimethyl succinyl betulinic acid group. These amendments do not affect the scope of the claims because chemists do not assign the broad meaning to the term "derivative" that is assigned by the Examiner. And Applicants never intended the term "derivative" to encompass compounds that are not considered to be members of the, e.g., betulin or betulinic acid groups of compounds.

According to the Federal Circuit, "[i]t is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Capon v. Eshhar*, 418 F.3d 1349, 1359, 76 U.S.P.Q.2d 1078, 1085 (Fed. Cir. 2005). In addition, when generic elements of a claim are so well known and thoroughly characterized in the art that their recitation alone is sufficient to convey distinguishing information regarding their identity, then the written description requirement for those elements is fully satisfied. *See Amgen Inc. v. Hoechst Marion Roussel Inc.*, 65 U.S.P.Q.2d 1385, 1398 (Fed. Cir. 2003).

Applicants further note that the Examiner's analysis of the written description requirement is flawed because it focuses improperly on an element of the claims that is not the point of novelty of the invention. Several recent cases from the Federal Circuit confirm that, for generic elements of a claim that are well known in the art and are not

themselves the point of novelty of a claimed invention, the written description requirement may be satisfied with respect to those elements by their recitation alone.

For example, in *Amgen*, the Federal Circuit held that a patent specification that disclosed only two species of vertebrate or mammalian cells nonetheless provided adequate written description support for method claims that involved the use of vertebrate or mammalian cells, generally. *See Amgen*, 65 U.S.P.Q.2d at 1398. According to the court:

> the claim terms at issue here are not new or unknown biological materials that ordinary skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO...*the words "vertebrate" and "mammalian" readily "convey[] distinguishing information concerning [their] identity" such that one of ordinary skill in the art could "visualize or recognize the identity of the members of the genus.*" Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus of vertebrate or mammalian cells, renders *Eli Lilly* listless in this case.

Id., 65 U.S.P.Q.2d at 1398. (internal citations omitted, emphasis added). The court's decision was based on two principle factors:

- That the claim terms at issue ("vertebrate" and "mammalian") did *not* refer to new or unknown biological materials that ordinary skilled artisans would easily miscomprehend; and
- That the words "vertebrate" and "mammalian," as used in the claims, readily conveyed distinguishing information concerning their identity such that one of ordinary skill in the art could visualize or recognize the identity of members of the genus.

When the reasoning of *Amgen* is applied in the context of the present claims, it is clear that the written description requirement is more than adequately satisfied for

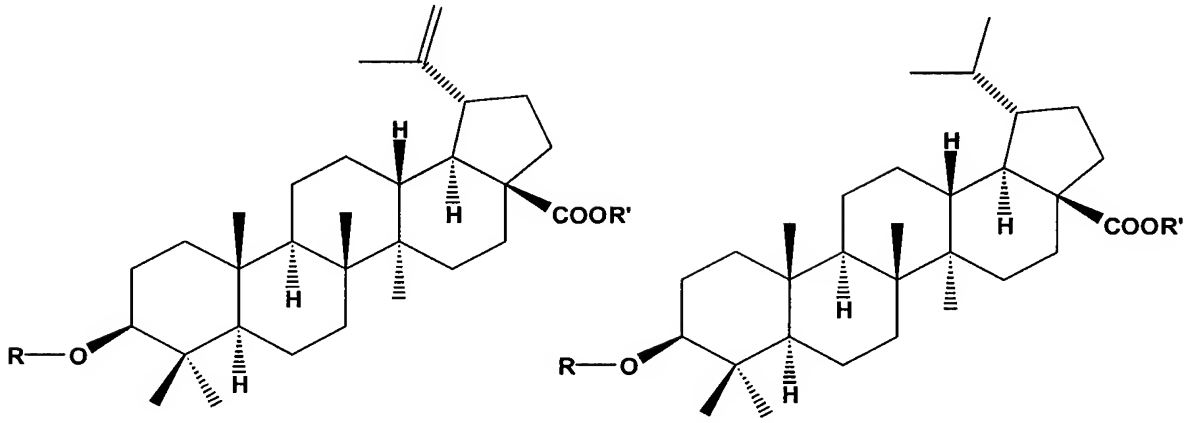
members of the betulin and betulinic acid groups, or other recited groups, that inhibit p25 (CA-SP1) processing to p24 (CA).

First, the term "member of the betulin or betulinic acid group of compounds" like the terms "vertebrate" and "mammalian," does not refer to new or unknown materials that ordinary skilled artisans would easily miscomprehend. As noted in the specification, betulin and betulinic acid compounds that inhibit CA-SP1 processing, were known. For example, the specification states:

> Previously, betulinic acid . . . [was] isolated from *Syzigium claviflorum* and . . .determined to have anti-HIV activity. Betulinic acid . . . exhibited inhibitory activity against HIV-1 replication in H9 lymphocyte cells with EC50 [value] . . of 1.4 μM . . . , and therapeutic index (T.I.) . . . 9.3 . . . . Hydrogenation of betulinic acid yielded dihydrobetulinic acid, which showed slightly more potent anti- HIV activity with an EC50 value of 0.9 and a T.I. value of 14 (Fujioka, T., *et al., J. Nat. Prod. 57*:243-247 (1994)). Esterification of betulinic acid with certain substituted acyl groups, such as 3',3'-dimethylglutaryl and 3',3'-dimethylsuccinyl groups produced derivatives having enhanced activity (Kashiwada, Y., *et al., J. Med. Chem. 39*:1016-1017 (1996)). Acylated betulinic acid and dihydrobetulinic acid derivatives that are potent anti-HIV agents are also described in U.S. Patent No. 5,679,828. Anti-HIV assays indicated that 3-O-(3',3'-dimethylsuccinyl)-betulinic acid and the dihydrobetulinic acid analog both demonstrated extremely potent anti-HIV activity in acutely infected H9 lymphocytes with EC50 values of less than 1.7 x 10-5 μM, respectively. These compounds exhibited remarkable T.I. values of more than 970,000 and more than 400,000, respectively.

Specification, paragraph [0012], pp. 5-6. The specification also describes numerous examples of betulins and betulinic acids--often referred to in the specification as derivatives--for example, at paragraph [0081]:

> Compounds useful in the present invention include, but are not limited to those having the general Formula ***I*** and ***II***:



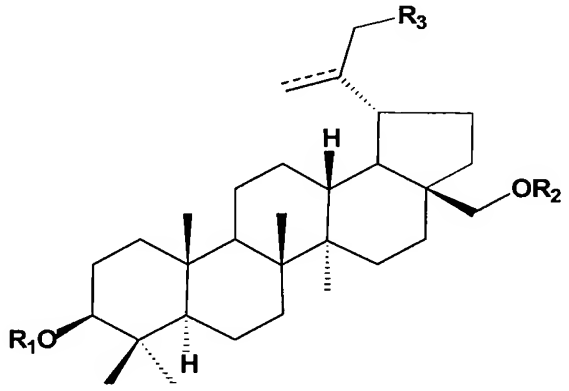
***I*: Derivatives of Betulinic Acid (left) and Dihydrobetulinic Acid (right),**

or a pharmaceutically acceptable salt thereof, wherein,

R is a C_2-C_{20} substituted or unsubstituted carboxyacyl,

R' is hydrogen or a C_2-C_{10} substituted and unsubstituted alkyl or aryl group.

Preferred compounds are those wherein R is one of the substituents in Table 2 and R' is hydrogen.



***II*: Derivatives of betulin and dihydrobetulin,**

or a pharmaceutically acceptable salt thereof, wherein,

R_1 is a C_2-C_{20} substituted or unsubstituted carboxyacyl,

R_2 is hydrogen or a C_2-C_{20} substituted or unsubstituted carboxyacyl; and

> R_3 is hydrogen, halogen, amino, optionally substituted mono- or di-alkylamino, or -OR_4, where R_4 is hydrogen, C_{1-4} alkanoyl, benzoyl, or C_2-C_{20} substituted or unsubstituted carboxyacyl;
>
> wherein the dashed line represents an optional double bond between C20 and C29.

Specification, paragraph [0081], pp. 28-29. The specification describes additional examples of these compounds in the text following paragraph [0081]. These compounds all have a betulin or betulinic acid backbone. Thus, the molecules identified as betulin or betulinic acid derivatives in the present application were not new or unknown materials.

Second, the claim term itself readily conveys distinguishing information concerning the identity of the recited compounds so that persons of ordinary skill in the art could recognize the identities of members of the genus. Persons of ordinary skill in the art would readily understand from the claim terms alone that the compounds used in the practice of the claimed methods (a) are members of, e.g., the betulin or betulinic acid groups of compounds, and (b) are capable of inhibiting CA-SP1 processing. Thus, a skilled person would be able to readily distinguish the compounds used in the practice of the claimed methods from compounds that fall outside the scope of the claim language (i.e., compounds that are not members of, e.g., the betulin or betulinic acid groups and/or that do not inhibit CA-SP1 processing).

Therefore, claims 1-7, 9-10, 12 and 82-84 and are adequately supported by the written description. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. 112, First Paragraph--Enablement

Claims 1-7, 9-10, 12-13 and 82-84 were rejected for allegedly failing to comply with the enablement requirement. The ground for the rejection appears to be the recitation of "derivative." Applicants respectfully traverse this rejection.

Concerning claim 13, Applicants note that this claim has never recited the term "derivative."

Concerning the remaining claims, as discussed above, they have been amended to omit the term "derivative." Applicants emphasize that, as understood by a chemist, the phrase "derivative of betulin or betulinic acid" does not encompass "a genus of unspecified compounds," as interpreted by the Examiner. Claim 1 now recites that the compound being administered is a member of the betulin group or betulinic acid group of compounds. Claim 12 now recites that the compound being administered is member of the dimethyl succinyl betulin group or dimethyl succinyl betulinic acid group of compounds.

Furthermore, the Examiner stated that insufficient correlation exists between in vitro and in vivo results. Applicants refer the Examiner to the Amendments filed January 22, 2007 and July 18, 2007; the arguments in both Amendments are incorporated herein. In the January 22 Amendment, Applicants discussed *Wands* factors such as the advanced state of the art in HIV-1 therapy, the breadth of the working examples in the present specification, and the fact that those of skill in the art appreciate that in the case of a viral target, as opposed to a cellular target, in vitro results and in vivo results are strongly correlated. In the July 18 Amendment, Applicants presented evidence that PA-

457 and PA-040 have entered into FDA-approved clinical trials for treatment of HIV-1 infection. These compounds are members of the compounds recited in claims 1 and 12.

Moreover, as mentioned in the January 22 Amendment, other members of the recited compounds were known compounds that had been found to have anti-HIV activity. Applicants assert that once artisans have determined that compounds, such as the recited compounds, have a particular therapeutic activity, then assays for pharmacokinetics, bioavailability, toxicity, etc., are routine in the pharmaceutical industry.

Further, the FDA and other experts in the field provide a copious amount of guidance for carrying out this routine experimentation, including guidance for extrapolating the results of in vitro and animal experiments to humans. A list of guidance documents available on the FDA website in December 2002 is attached (courtesy of the Internet Archive Wayback Machine; copy of search results enclosed). This list includes the following:

- Bioavailability and Bioequivalence Studies for Orally Administered Drug Products[:] General Considerations
- Antiretroviral Drugs Using Plasma HIV RNA measurements[:] Clinical Considerations for Accelerated and Traditional Approval
- Clinical Development and Labeling of Anti-Infective Drug Products
- Clinical Evaluation of Anti-Infective Drugs (Systemic)
- Preclinical Development of Antiviral Drugs
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products
- Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies in Vitro

- In vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling
- Population Pharmacokinetics
- Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications

Because a large body of guidance existed for performing the routine experimentation needed for FDA approval, it was not necessary for Applicants to include this guidance in the specification. What is known in the art is preferably not included in the application. MPEP 2164.05(b) at 2100-200, col. 1 (citing several decisions by the Court of Appeals of the Federal Circuit).

Therefore, claims 1-7, 9-10, 12-13 and 82-84 are enabled. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. 112, Second Paragraph--Definiteness

Claims 1-7, 9-10, 12 and 82-84 were rejected as allegedly being indefinite for reciting "derivative" or depending from a claim reciting "derivative." Applicants respectfully traverse the rejection.

Applicants have amended claims 1 and 12 to remove the recitation of "derivative." Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Applicants respectfully request an interview with the Examiner to discuss any outstanding rejections once she has had the opportunity to consider the present amendment and response.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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